PATENT
910000-2012

#19

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Kochevar et al.
Serial No.	:	09/781,577
Filed	:	February 12, 2001
For	:	PHOTOCHEMICAL TISSUE BONDING
Examiner	:	Thomas C. Barrett
Art Unit	:	3738

745 Fifth Avenue
New York, NY 10151

EXPRESS MAIL

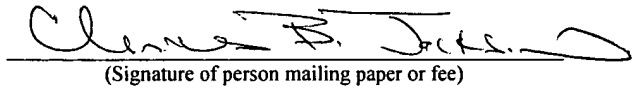
Mailing Label Number EV073692510US

Date of Deposit: April 10, 2003

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Service under 37 CFR 1.10 on the date indicated above and is addressed to the Honorable Commissioner of Patents and Trademarks (Box AF), Washington, DC 20231.

Charles B. Jackson

(Typed or printed name of person mailing paper or fee)



(Signature of person mailing paper or fee)

SUPPLEMENTAL DECLARATION FOR CORRECTION OF CITIZENSHIP

I, Dr. Robert W. Redmond, state that I was the Declarant of Declaration dated August 13, 2001 and submitted by my attorneys on August 28, 2001. I herein respectfully request to incorporate, by reference, the entire Declaration executed by me on August 13, 2001. In addition, I hereby assert that my citizenship should read "United Kingdom", and respectfully request that this inadvertent omission be corrected and entered into the file.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are made are

punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 3/26/2003

Dr. Robert W. Redmond

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Kochevar et al.
Serial No.	:	09/781,577
Filed	:	February 12, 2001
For	:	PHOTOCHEMICAL TISSUE BONDING
Examiner	:	Thomas C. Barrett
Art Unit	:	3738

745 Fifth Avenue
New York, NY 10151

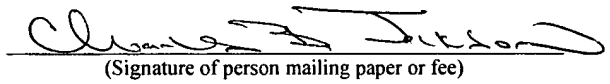
EXPRESS MAIL

Mailing Label Number: EV073692510US

Date of Deposit: April 10, 2003

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Service under 37 CFR 1.10 on the date indicated above and is addressed to: Assistant Commissioner for Patents, Washington, DC 20231.

Charles B. Jackson
(Typed or printed name of person mailing paper or fee)


(Signature of person mailing paper or fee)

COMMUNICATION

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Applicants hereby submit a Declaration under 37 C.F.R. 1.131 signed by Irene E. Kochevar, Robert W. Redmond, and Dimitri Azar, along with a Supplemental Declaration for Correction of Citizenship signed by Robert W. Redmond. Also submitted herewith is a newly executed Declaration for Patent Application and Power of Attorney, signed by all of the inventors.

The enclosed Supplemental Declaration serves only to correct the citizenship of one of the inventor's, such that it is properly recorded as United Kingdom.

Also enclosed is an executed assignment, signed by Dimitri Azar, and assignment recordation cover sheet, together with a check in the amount of $40.00 in payment of the fee therefor. Applicants are submitting this Assignment in order to correctly identify the assignee for the inventive contributions made by Dimitri Azar to the present invention.

It is believed that no fee is occasioned by entry of this paper, however, the Commissioner is hereby authorized to charge any necessary fee, or credit any overpayment in fees, to Deposit Account 50-0230.

A prompt issuance of the granted patent is respectfully requested.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP
Attorneys for Applicants

By: Amy Leahy
Amy Leahy, Ph.D.
Reg. No. 47,739
(212) 588-0800

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Kochevar et al.
Serial No.	:	09/781,577
Filed	:	Feb 12, 2001
Title	:	PHOTOCHEMICAL TISSUE BONDING
Examiner	:	Thomas C. Barrett
Art Unit	:	3738

745 Fifth Avenue
New York, NY 10151

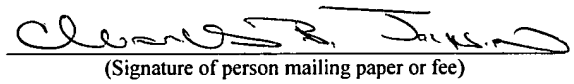
EXPRESS MAIL

Mailing Label Number: EV073692510US

Date of Deposit: April 10, 2003

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Service under 37 CFR 1.10 on the date indicated above and is addressed to the Honorable Commissioner of Patents and Trademarks (Box AF), Washington, DC 20231.

Charles B. Jackson
(Typed or printed name of person mailing paper or fee)


(Signature of person mailing paper or fee)

DECLARATION OF IRENE KOCHEVAR, DIMITRI AZAR AND ROBERT REDMOND UNDER 37 C.F.R. §1.131

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

We, Irene Kochevar, Dimitri Azar and Robert Redmond, hereby declare and state as follows:

1. We, Irene Kochevar, citizen of the United States of America, Robert Redmond, citizen of the United Kingdom, and Dimitri Azar, citizen of Lebanon, are each a named inventor in the above-identified application ("the present application" or "the '577 application").

2. We, Irene Kochevar and Robert Redmond, were each an employee of The General Hospital Corporation, Boston, MA, and I, Dimitri Azar, was an employee of the Massachusetts Eye and Ear Infirmary, at the time of the conception and reduction to practice of the subject matter of said application in the United States. At the time of conception, we were all under an obligation to assign U.S. Application Serial No. 09/781,577 ("the '577 application") and the invention thereof to our respective employers.

3. During our employment in the U.S. at either The General Hospital Corporation or the Massachusetts Eye and Ear Infirmary, we conceived of the subject matter of the '577 application, filed February 12, 2001 and claiming priority to U.S. Application Serial No. 60/181,980 ("the '980 application"), filed on February 11, 2000, in the United States prior to March 1999, the publication dates of Melki et al., "Photochemical Tissue Repair (Welding) of Clear Cornea Incision," March (1999) IVOS, Vol440, No. 4:s340, Abstract 1803-B711 ("Melki") and Mulroy et al., "Photochemical Tissue Bonding for Corneal Repair and Transplants," 27th Annual Meeting of the American Society for Photobiology, Abstract MPM-E21 March (1999) ("Mulroy").

4. The conception in the U.S. of the subject matter of the '577 application is evidenced, at least in part, by a draft grant application, which proposed experiments designed to improve the methods for "securing skin grafts to wound beds and to introduce a new method for repairing blood vessels." Specifically, the draft grant application indicated an experiment plan to "attach skin graft material to a prepared tissue bed using photochemical tissue bonding" and to "join several blood vessels using photochemical tissue bonding and a biocompatable sleeve."

5. From the time of conception of the invention, we diligently worked on the invention, including developing additional embodiments of the invention, in the U.S., and promptly and diligently forwarding written descriptions of such additional embodiments to The General Hospital's attorney in the U.S., for the preparation and filing of the '980 and subsequently, the '577 applications.

6. Thus, the subject matter of the '980 and '577 applications was conceived by us in the U.S. prior to at least March 1, 1999 and was diligently pursued by us in the U.S., until a reduction to practice was achieved on at least February 11, 2000 by the filing of said '980 application (if not earlier as described in the supporting and other documents). Accordingly, we are advised and therefore believe that this application is entitled to antedate Melki and Mulroy

within the purview of 37 C.F.R. §1.131. We also respectfully request that Melki and Mulroy be considered as antedated and as not available as prior art against the present application.

7. We further declare that all statements made herein are true and that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the application or any patent issuing thereon.

7 April 2003	Irene E Kochevar
Date	Irene Kochevar, Ph.D.
_____	_____
Date	Robert Redmond, Ph.D.
_____	_____
Date	Dimitri Azar, Ph.D.

within the purview of 37 C.F.R. §1.131. We also respectfully request that Melki and Mulroy be considered as antedated and as not available as prior art against the present application.

7. We further declare that all statements made herein are true and that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the application or any patent issuing thereon.

Date	Irene Kochevar, Ph.D.
Date	Robert Redmond, Ph.D.
Date 4/7/03	Dimitri Azar, Ph.D.

within the purview of 37 C.F.R. §1.131. We also respectfully request that Melki and Mulroy be considered as antedated and as not available as prior art against the present application.

7. We further declare that all statements made herein are true and that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the application or any patent issuing thereon.

Date	Irene Kochevar, Ph.D.
3/27/03 Date	Robert Redmond, Ph.D.
Date	Dimitri Azar, Ph.D.

A photochemical approach to tissue bonding

I.E. Kochevar, R.W. Redmond

Aims: The long range goals of this project are to improve the methods for securing skin grafts to wound beds and to introduce a new method for repairing blood vessels. Specifically we plan to:

1. Attach skin graft material to a prepared tissue bed using photochemical tissue bonding.
   a. Assess the ability to form bonds between dermal tissue surfaces.
   b. Optimize the dye and laser conditions for bonding dermal tissue surfaces.
   c. Utilize animal model of split thickness skin grafts to evaluate photochemical tissue bonding.

2. Join severed blood vessels using photochemical tissue bonding and a biocompatable sleeve.
   a. Evaluate the bonding produced between collagen-containing biomaterials and the adventitial surface of blood vessels.
   b. Optimize the dye and laser conditions for bonding of biomaterials to blood vessels.
   c. Utilize an animal model for joining of blood vessels using photochemical tissue bonding.

Background

Photochemical tissue bonding (PTB) is produced by applying a photosensitizing dye, which adheres to the surfaces to be bonded, and then activating the dye with visible light. The photoactivated dye induces the instantaneous formation of many strong covalent bonds between protein molecules in the two surfaces. Subsequent tissue remodeling occurs to produce the final repaired tissue. Typically, visible light from a laser is used but conventional intense light sources may also be employed.

The mechanism underlying PTB differs from the more commonly used photothermal tissue welding which involves thermal denaturation of proteins and formation of weaker non-covalent bonds. Photochemical tissue bonding joins tissue surfaces together without heat and the associated problems of peripheral tissue damage.

We are currently studying the application of PTB to repair of small corneal incisions and to corneal transplantations in rabbit eyes. In experiments using enucleated rabbit eyes, a dye (rose bengal) was applied to small corneal incisions, which were then treated with cw 514 nm argon ion laser radiation. The incisions were rapidly sealed and acceptable bursting pressures were produced. The dye and light combinations are now being optimized and in vivo experiments on both incision closure and corneal transplantation are beginning. These studies demonstrated that, in principle, PTB is effective for collagen-containing tissues.

Photochemical tissue bonding may be a useful addition to the techniques now available for immobilizing grafts onto recipient beds duirng the revascularization phase. The major

advantages of PTB are that it is rapid, can be used for surfaces with varying contours, and is potentially bactericidal.

For repairing severed blood vessels, the major advantages of PTB are that it is rapid and reduces or eliminates the need for sutures in very small diameter blood vessels.

Experimental Design and Methods

The overall plan for this project is that the in vitro experiments necessary assess the ability to form bonds between tissue surfaces (graft beds, blood vessels) and tissue (for skin grafts) or biological compatible materials (skin grafts and blood vessels) will be done at the Wellman Laboratories. As these aspects are being developed, ISR personnel (fellow?) will consult both by traveling to Wellman and discussions in order to infuse medical expertise on these specific topics. When the photochemical parameters become better defined for the various types of tissue and tissue substitutes, experiments using animal models will be carried out at ISR. After the initial experiments, it is anticipated that these two aspects will be carried out concurrently since the types of information obtained are complementary and synergistic.

The initial in vitro experiments will be designed to identify the best dye and laser conditions to bind collagen-based biosynthetic dressings to excised animal dermis and excised animal blood vessels. (We need help in deciding which systems will lead to results that will be most useful for translating into in vivo animal models.)

As information becomes available from these experiments, ISR researchers would begin to evaluate the efficacy of PTB for partial and full thickness skin grafts in rats and guinea pigs. Further in vivo studies would meshed partial thickness skin grafts, large neck artery grafts in goats and surgical closures of internal organ and surface operations.

Budget:

Personnel:

	Percent effort
Kochevar	5
Redmond	5
Wellman Fellow	100
Wellman technician	50

Travel

ISR fellow	multiple trips/week long stays
Wellman personnel	4 trips/year to ISR

Supplies